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A Random Model for Tumor Immunobiomechanism: Theoretical Implication for Host-Defense Mechanism

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腫瘍免疫機構に関する確率モデル:
生体防御に関する理論的示唆
道工 勇
埼玉大学教育学部数学教室

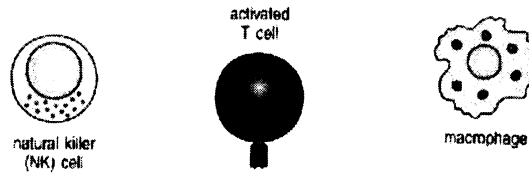
The purpose consists in construction of a mathematical model that describes the host-defense mechanism against cancer. Roughly speaking, there are two distinct methods in mathematical modelling for cancer cells, such as the method by a deterministic model and the method by a stochastic model. In this article, based upon the latter method, we propose an immune response model against cancer as a mathematical model of branching particle system, and grasp the effects of immunity as the reflective extinction of a superprocess arising by taking the limit of the system. Ordinarily, normal cells are transformed into irregular ones by some reasons, and the tumorigenic process proceeds. In concord with that, a group of immune cells invoke immune response, and in so doing they accomplish their important errand of host-defense mechanism. We focus our mind especially on the immune response both in the transformation period of cell and in the proliferation period of cancerated cell, and propose a stochastic model that is able to describe the cytotoxic actions of effectors against cancer cells. Those effectors are supposed to be NK (natural killer) cells, cytotoxic T cells, and activated macrophages, etc. Analyzing the model mathematically, we study the qualitative properties of the biological phenomena related to immune response, and we are aiming at explaining an extraordinary phenomenon such as the saturation of immune effectiveness, from the viewpoint of model theory. In our previous research [6] we introduced the immigration rate $q > 0$ (a positive constant) as the cytotoxic intensity of effectors against cancer. In the present paper we improve this point and propose a more elaborate model that can describe the effects by those effectors, depending on the location in accordance with the environmental changes. We finally consider the extinction property of the proposed model, which corresponds to a key physiological phenomenon of immune response relative to the effectors.

本研究の目的はがん細胞に対する免疫反応を記述する数理モデルの構築にある。がん細胞に対する数理モデリングの手法は、大雑把に言って確定モデルか確率モデルによる記述の2つに大別される。ここではがん細胞の免疫応答を後者の立場に基づき分枝粒子系の数理モデルとして提案し、免疫能の働きをその極限の超過程の消滅性の反映として捉える。通常細胞が何らかの要因で形質転換して細胞のがん化過程が進行する。それに対して免疫細胞群は免疫応答作用することで、生体防御の重要な役割を担っている。細胞の形質転換期及びがん化細胞の無秩序増殖期における免疫応答に焦点を当て、NK細胞、キラーT細胞、マクロファージなどのエフェクターによるがん細胞に対する細胞障害性の働きを記述する確率モデルを提案し、そのモデルを数理的に解析することにより、免疫作用に関わる現象の定性的性質や特異現象に対するモデル論的な説明を補助的に提供することを目指す。前研究 [6] においては、エフェクターのがんへの細胞障害性の強さを移入率 $q > 0$ (正定数) として導入した。本研究ではこの点を改良して、場所ごとに異なり個体ごとの環境変化に応じたエフェクター効果を記述出来るモデルに関して、キーとなる生理現象に対応する消滅性について考察する。

1 Introduction

We are aiming at mathematically modelling the immune response against cancer cells. Ordinarily, some of normal cells are transformed into irregular ones by several reasons, such as chemicals, carcinogens, carcinogenic virus and bacteria, DNA replication error, DNA repair disorder, chromosomal end centromere disorder, radiation and so on, and the tumorigenic process proceeds. In concord with that, a group of immune cells invoke the immune response against canceration, accomplishing an important errand of host-defense mechanism in the living body. The effectors are supposed to be NK (natural killer) cells, cytotoxic T cells, and activated macrophages, etc. We focus especially on the immune response both in the transformation period of cell and in the proliferation period of cancerated cell, and propose a random model that is able to describe the cytotoxic effects by a bunch of effectors against cancer cells. Analyzing

the model mathematically, we provide with a complementary explanation of qualitative properties and peculiar phenomena relative to immune actions from the viewpoint of modelling theory.



⊠ 1: A group of effectors

Recently the system biological researches on cancer have made a remarkable progress, cf. Wang (2010) [16]. Accompanying this rapid progress, the modelling theoretical researches, simulation and numerical analysis have become in full activity now, that are driving for illuminating the biological dynamism of cancer cells and mechanism of cancer-specific phenomena, based upon the standpoint of mathematical physiology, cf. Wodarz and Komarova (2005) [18]. In this paper we may adopt stochastic modelling approach [14] to grasp the immune response against cancer as a mathematical model of branching particle system, and to consider the effectiveness of immunity as a reflection of extinction property on superprocesses. In [1] we considered a formulation of catalytic processes applicable to filaments and catalysts in physiology and biochemistry, and studied asymptotic behaviours of solutions to related equations. While, in [2] we investigated a special class of stochastic processes related to chemical reaction of the medicinal, and proved the existence and uniqueness theorem for measure-valued processes which is able to describe the increase or decrease of a branching particle system in number according to whether the environment is good or not.

2 Prerequisite from immunobiology

2.1 Network of immune system

The immune system in the living body is regulated by the effector-induction protocol. It is known that various kind of effectors (such as T cells, B cells, NK cells, NKT cells, dendritic cells, and macrophages, etc.) form a very complicated network, and that there is a possibility that it provokes a positive and/or negative immune response for/against cancer cells. Our main concern is antitumor immune response, and NK cells, NKT cells and T cells have to do with the immune surveillance for cancerated cells. On the other hand, the same bunch of immune cells reveal antitumor immune effects against swollen cancer cells. The dendritic cell works as an antigen-presenting cell (APC) in the living body, that is to say, it processes a tumor antigen, activates an antitumor T cell, and plays an important role in urging a CTL to propagate. The macrophage is an immune cell which possesses a strong cytotoxicity, however in the living body with a kind of cancer it works as an immune suppressor or as an antitumor effector according to the physiological situation there. More precisely, in the network of immune system, first of all a cancer cell with tumor antigen is taken in by a professional APC with phagocytosis, then the APC presents a cancer antigen to a CD8+ T cell via a co-stimulatory molecule with the help of CD4+ helper T cell, while the CD8+ T cell will be able to recognize the antigen via conjugation with co-receptor, being urged to specialize into a CTL by a small cloud of cytokines emitted by a CD4+ helper T cell. When the specified

CD8+ T cell next encounters a cancer cell with the same antigen, then the CTL may recognize it as a target and executes a killing of the cancer cell by cytotoxicity [13].

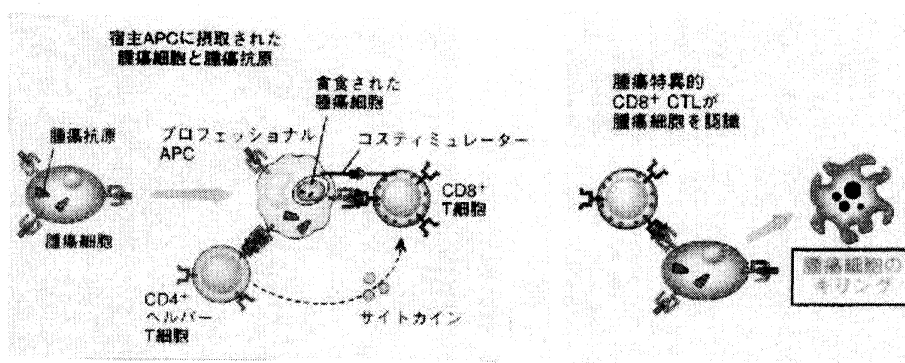


図 2: Induction and effectual phase of CTL

2.2 Monoclonal antibody and antitumor immune response

Generally, the monoclonal antibody is produced by an immortalized hybridoma (= a sort of hybrid cell) which is an antibody-forming cell (= B cell) of target antigen-immunized mouse, amalgamated with a special myeloma cell. The monoclonal antibody is much more specific than the blood serum antibody (or polyclonal antibody), moreover there is a merit that it is possible to produce largely uniform and identically specific antibodies. This cell fusion technique applied to this production of hybridoma was established in 1975 by G. Köhler and C. Milstein, and they won the Nobel Prize in Physiology and Medicine in 1984 for this exploit. Recently plenty of attempts have been made that the human-type monoclonal antibody produced from human cells is used to the cure for cancer. For instance, outstanding antitumor effects have been recently confirmed for two exceptional antibodies among monoclonal antibodies produced from human-cancer-cell-immunized animals of different species, such as the antibody of Her2 of breast cancer and antibody of CD20 of lymphoma, see e.g. the report of JACI (2011) [11].

The elucidation of molecular biological mechanism for antitumor immune response has been rapidly promoted in these days. However, it is certain that the actual situation is really complicated, and also that the unknown parts are not few. A group of immune cells (such as dendritic cells, NK cells, NKT cells, and macrophages) carries the innate immune response on its back in the early stage, and induces the acquired (adaptive) immune response of T cells and B cells being a system with high output rate by antigen-specified proliferation, through the secretion of cytokines and the presentation of antigen. Although the antitumor effect is observed in the administration of monoclonal antibody via mouse, it is not clear unexpectedly what the antitumor immunity via antibodies produced by the patient means in fact. The T cell plays an extremely important role for tumor rejection in plenty of animal tumor models and human malignant melanoma [15]. In the immune response of T cell, the T cell receptor specifically recognizes the tumor antigen peptide-MHC complex on the cancer surface, and the T cell secretes cytokines and injures the cancer cell directly. There are two kinds of T cells in the class of tumor-reactive T cells; one is the CD8+ T cell that recognizes the MHC class I-peptide complex, and the other is the CD4+ T cell that recognizes the MHC class II-peptide complex. The CD8+ T cell has to do directly with the recognition of cancer cell. On the other hand, the CD4+ T cell has to do with the induction and maintenance of CD8+ T cell, and is also concerned with the effector-activation of

macrophage and the collection or wandering interception of antitumor CD8+ T cell within the tumor area, see also e.g. Murphy et al. (2008) [12].

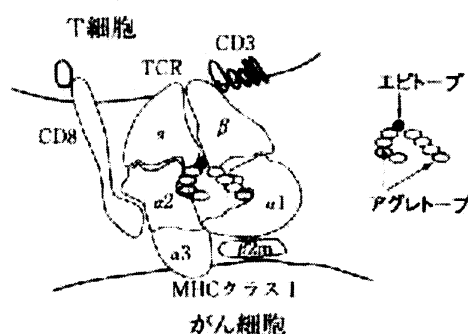
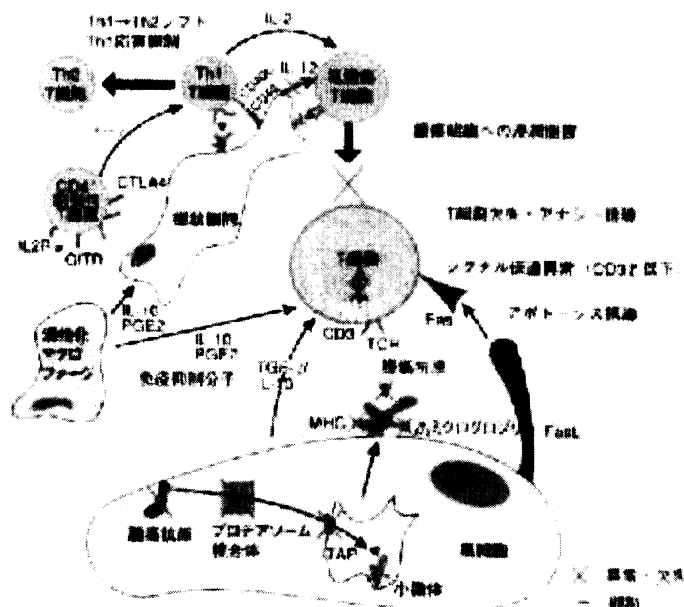


図 3: Antitumor cytotoxicity of T cell

2.3 Tumor escape mechanism

It is reported that the cancer cell possesses the so-called escape mechanism from various kinds of immune responses. Since the cancer cell has malfunction in the molecule that is concerned directly with antigen recognition by T cell, the cancer cell is capable to escape from the immune surveillance without recognition by T cell. For example, the malfunction in the molecule can be found in tumor antigen, MHC, $\beta 2$ micro-globulin, and various molecules related to the antigen processing.



Furthermore, the cancer cell is able to intercept the action of immunity by promoting the secretion of

immune suppressors. Those suppressors are, for instance, TGF- β and IL-10 secreted from the cancer, and IL-6 and PGE2 emitted from the macrophage (which is urged to secrete by the cancer cell). Except the above avoidance, we can list below some other factors: weakening of Th1 response by Th2 displacement, signal transduction disorder of T cell, induction of tumor-antigen-specific immunological tolerance, induction of antitumor immune suppressive T cell, T cell apoptosis induction by FasL appearance on a cancer cell, local environment that intercepts collection of T cells in the tumor tissue, and so on. See e.g. Weinberg (2007) [17]; see also [15].

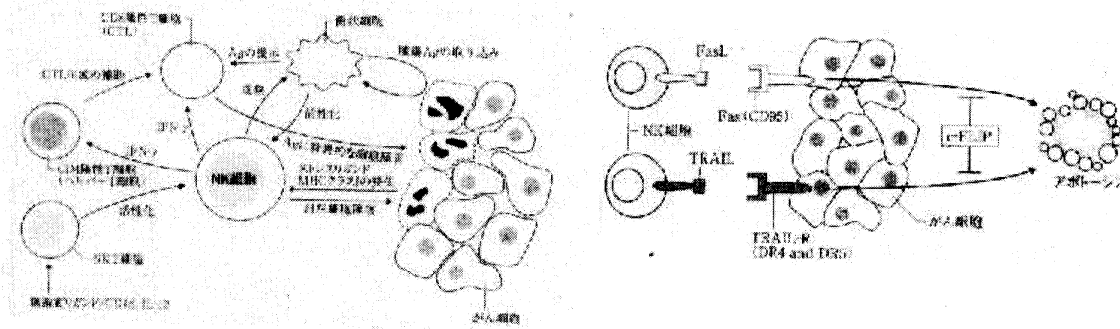


図 4: Mechanism of antitumor effectors

3 Random model for immune response

3.1 Proliferation process of cancer cells

When the tumorigenic process proceeds, normal cells are transformed into irregular ones by some reasons and are cancerated, and they repeat disorder proliferation peculiar to the cancer because of continual emission of false proliferation signals by malfunctioned oncogenes and tumor suppressor genes. On the other hand, the cancer cell is preyed or destroyed by effectors (a group of immune cells such as NK cells and so on) by virtue of the immune surveillance mechanism in a living body. Then, taking them all into consideration, we introduce the natural number valued random variable $N_n : \Omega \rightarrow \mathbb{N}$ for each n , which means the total number of cancer cells in the n -th generation. We assume that there is a sequence $\{\gamma_n\}_n$ of positive numbers such that

$$\gamma_n \rightarrow \gamma \in \mathbb{R}_+ \quad (n \rightarrow \infty)$$

and also that

$$E[\xi_n] = 1 + \frac{\gamma_n}{n}, \quad \text{Var}(\xi_n) = \sigma_n^2 \rightarrow \sigma^2 \quad (n \rightarrow \infty)$$

where ξ_n is the number of offsprings generated by the n -th generation. This implies that the branching particle system has a clear tendency to increase in number. When we suppose that for each cell, the proliferation or division occurs independently at a random time, we introduce the branching rate $n\lambda$ ($\lambda > 0$), which means the accelerated increase rate for the number of cancer cells. We adopt a model by a branching particle system as a proliferation process for cancer.

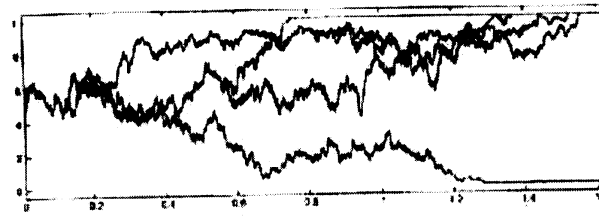


図 5: Trajectories of branching process

3.2 Spatial movement of cancer

Since we have only to describe the immune response in a locally limited tissue, the region in question is restricted to a comparatively small area. So that, it suffices to consider the model in a bounded domain $D \subset \mathbb{R}^d$ with $d = 3$. For N_n pieces of cancer cells in the n -th generation, each cancer cell is supposed to start at the initial point $x_i^{(n)} \in \mathbb{R}^d$ ($i = 1, 2, \dots, N_n$). While, it is considered that the target cell (= the cancer cell) moves little in the early stage, namely in the transformation period of cell, and also that in the proliferation period of cancerated cell it may diffuse and expand as if the liquid should seep through a leather bag because of a superfluity of proliferated cancer cells. Hence, we regard it as a diffusion with diffusion coefficient $k(\varepsilon)$ depending on a small parameter ε (> 0). The diffusion operator is defined as $L_\varepsilon = k(\varepsilon)\Delta$, where Δ is the Laplacian.

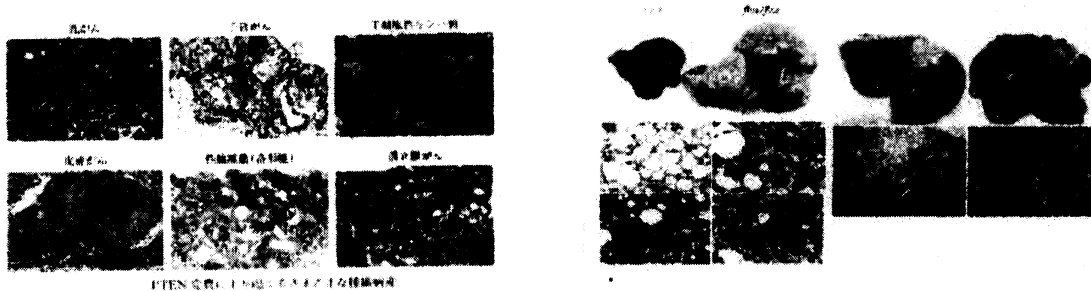


図 6: Various kinds of cancer cells

3.3 Cytotoxicity of effectors

In our model the effectors are supposed to be NK cells, killer T cells, macrophages among a group of immune cells, and we will take the cytotoxicity of these effectors against cancer into account. In the previous paper [6], the previous report [4] or the previous announcements [3] (see also [5]), we introduce a deterministic emigration rate $q(> 0)$ (a positive constant) in the terminology of the theory of stochastic processes, which expresses the intensity of cytotoxicity by effectors against cancer. Although one may find it interesting as the first random model, it is not necessarily desirable to treat it like a simple and poor model, in order to imitate the effects of immune response by effectors against cancer from the viewpoint of the modelling theory as well as from the standpoint of future simulation analysis. In this article we improve this point and propose a more elaborate model, which can describe the effects by those effectors,

depending on the location in accordance with the environment changes. There are three methods in the improvement. That is, it means that instead of the positive constant q , we adopt a (random) function q like:

$$(i) q(x), x \in D; \quad (ii) q(\omega) \text{ or } q(\omega, x), \omega \in \Omega; \quad (iii) q(t, \omega), \omega \in \Omega.$$

In the model (i) the intensity of cytotoxicity q depends on the location $x \in D$, which means that the intensity $q(x)$ varies as the environment changes, and it strengthens or weakens according to the good or bad environment. In the second new model the parameter ω expresses the environmental change independent of the sample ω' which comes from the original stochasticity of the branching model. The latter case $q(\omega, x)$ just corresponds to the case $q(\omega)$ depending on the location. In the model (iii) the time evolution of $q(\omega)$ can also be described. As a matter of fact, we can realize it as the choice of branching rate $\alpha(x)$ and branching mechanism $\beta(x)$ depending on the location (or ω, t), for example.

3.4 Superprocess under the limiting procedure

Under the above-mentioned settings, we propose a random model for the target cancer cells:

$$X_t^{(n)} = \frac{1}{n} \sum_{i=1}^{N_n(t)} \delta_{x_i^{(n)}(t)} \quad (1)$$

where $x_i^{(n)}(t)$ is the location of the i -th cancer cell in the n -th generation at time t , and $N_n(t)$ denotes the total number of cancer cells alive at time t . Eq.(1) is the quantity related to an empirical measure, expressing the state of the cancer at time t . For instance, the qualitative property of a random walk is well reflected by its limiting process, say, the Brownian motion. Likewise, the qualitative property of an aggregate of cancer cells can be thought to be reflected by its limiting process X_t . On this account, we will analyze the superprocess X_t in what follows.

4 Analysis on the limiting process

Let $C = C(\mathbb{R}^d)$ be the space of continuous functions on \mathbb{R}^d . When C_b denotes the set of bounded continuous functions on \mathbb{R}^d , then C_b^+ is the set of positive members g in C_b . Let $\langle \mu, f \rangle = \int f d\mu$, and $M_F = M_F(\mathbb{R}^d)$ is the space of finite measures on \mathbb{R}^d . We denote an L_ε -diffusion process by $\Xi = \{\xi, \Pi_{s,a}, s \geq 0, a \in \mathbb{R}^d\}$. Then $K \equiv K(dr)$ is the associated continuous additive functional (CAF), and we assume that K lies in the Dynkin locally admissible class of CAF, and we write it as $K \in \mathbb{K}^\eta$ (some $\eta > 0$). Then a superprocess $\mathbb{X} = \{X, \mathbb{P}_{s,\mu}, s \geq 0, \mu \in M_F\}$ with branching rate functional K (or (L, K, μ) -superprocess) can be characterized as a continuous M_F -valued time-inhomogeneous Markov process $X = \{X_t\}$ with Laplace functional

$$\mathbb{P}_{s,\mu} e^{-\langle X_t, \varphi \rangle} = e^{-\langle \mu, v(s,t) \rangle}, \quad 0 \leq s \leq t, \quad \mu \in M_F, \quad \varphi \in C_b^+.$$

Here the function v is uniquely determined by the log-Laplace equation

$$\Pi_{s,a} \varphi(\xi_t) = v(s,a) + \Pi_{s,a} \int_s^t v^2(r, \xi_r) K(dr), \quad 0 \leq s \leq t, \quad a \in \mathbb{R}^d.$$

We need Dynkin's Historical Superprocess. $\mathbb{C} = C(\mathbb{R}_+, \mathbb{R}^d)$ denotes the space of continuous paths on \mathbb{R}^d with topology of uniform convergence on compact subsets of \mathbb{R}_+ . To each $w \in \mathbb{C}$ and $t > 0$, $w^t \in \mathbb{C}$ expresses the stopped path of w , and \mathbb{C}^t is the totality of all these paths stopped at time t . To every $w \in \mathbb{C}$, putting $\tilde{w}_t = w^t$, $t \geq 0$, we associate the corresponding stopped path trajectory \tilde{w} . The image of L_ε -diffusion w under the map $: w \mapsto \tilde{w}$ is called the L_ε -diffusion path process. We define

$\mathbb{C}_R^\times \equiv \mathbb{R}_+ \hat{\times} \mathbb{C} = \{(s, w) : s \in \mathbb{R}_+, w \in \mathbb{C}^s\}$. We consider the set $M(\mathbb{C}_R^\times) \equiv M(\mathbb{R}_+ \hat{\times} \mathbb{C})$ of measures γ on $\mathbb{R}_+ \hat{\times} \mathbb{C}$ which are finite, if restricted to a finite time interval. Suppose that K is a positive CAF of ξ . Then Dynkin's historical superprocess (1991)

$$\tilde{\mathbb{X}} = \{\tilde{X}, \tilde{\mathbb{P}}_{s,\mu}, s \geq 0, \mu \in M_F(\mathbb{C}^s)\}$$

is defined as a time-inhomogeneous Markov process with state $\tilde{X}_t \in M_F(\mathbb{C}^t)$, $t \geq s$, with Laplace functional

$$\tilde{\mathbb{P}}_{s,\mu} e^{-\langle \tilde{X}_t, \varphi \rangle} = e^{-\langle \mu, v(s,t) \rangle} \quad 0 \leq s \leq t, \quad \mu \in M_F(\mathbb{C}^s), \quad \varphi \in C_b^+(\mathbb{C})$$

where v is uniquely determined by the log-Laplace type equation

$$\tilde{\Pi}_{s,w_s} \varphi(\tilde{\xi}_t) = v(s, w_s) + \tilde{\Pi}_{s,w_s} \int_s^t v^2(r, \tilde{\xi}_r) K(dr), \quad 0 \leq s \leq t, \quad w_s \in \mathbb{C}^s.$$

Theorem 1. *Let $K \in \mathbb{K}^\eta$ and $\mu \in M_F$ with compact support. Then there exists an (L, K, μ) -superprocess*

$$\mathbb{X} = \{X, \mathbb{P}_{s,\mu}, s \geq 0, \mu \in M_F\}$$

with branching rate functional K .

Theorem 2. *There exists a Dynkin's historical superprocess*

$$\tilde{\mathbb{X}} = \{\tilde{X}, \tilde{\mathbb{P}}_{s,\mu}, s \geq 0, \mu \in M_F(\mathbb{C}^s)\}.$$

In the previous work [6] (see also [3–5]) we have recognized that the extinction property of superprocesses is very important in the model theory. Especially as far as local extinction is concerned, it is of extreme interest and importance because it just corresponds to the situation that the cancer cells are expelled locally from the cancerated area by the immune effects of effectors.

Since the initial measure $\mu \in M_F$ has a compact support, it follows from the argument of compact support property (cf. Dawson-Mueller : Ann Prob 23 (1995)) that the range $\mathfrak{R}(X)$ of X is compact. Under the historical superprocess setting $\tilde{X}_t(dw)$, we define

$$\mathbb{C}_M = \{w \in \mathbb{C} : |w_s| < M, \forall s \geq 0\}$$

for $M \geq 1$. By the compact support property, we have

$$\lim_{K \rightarrow \infty} \inf_{t \geq 0} \tilde{\mathbb{P}}_{0,\mu} \left(\text{supp}(\tilde{X}_t) \subseteq \mathbb{C}_M \right) = 1, \quad \mathbb{P} - \text{a.a.} \omega.$$

Proposition 3. *For $K \in \mathbb{K}^\eta$*

$$\lim_{t \rightarrow \infty} \tilde{\mathbb{P}}_{0,\mu}(\tilde{X}_t \neq 0, \quad \text{and} \quad \text{supp}(\tilde{X}_t) \subseteq \mathbb{C}_M) = 0.$$

Finally, through the projection technique (cf. Dawson-Perkins (1991); Dôku (2003)) we obtain

Theorem 4. (Extinction property) *Let $d = 1$ and $\mu \in M_F$ with compact support. Then*

$$\mathbb{P}_{0,\mu}(X_t = 0 \quad \text{for some} \quad t > 0) = 1.$$

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